ACUTE TOXICITY SUMMARY

METHYLENE CHLORIDE

(dichloromethane, methylene dichloride)

CAS Registry Number: 75-09-2

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level	**14,000 μg/m³**
Critical effect(s)	subtle impairment of the central nervous system
Hazard Index target(s)	Nervous System

II. Physical and Chemical Properties (HSDB, 1994 except as noted)

Description	colorless liquid
Molecular formula	CH_2Cl_2
Molecular weight	84.93
Density	1.32 g/cm^3 @ 20°C (ACGIH, 1991)
Boiling point	39.75°C
Melting point	-95.1°C (ACGIH, 1991)
Vapor pressure	400 mm Hg @ 24.1°C
Flashpoint	unknown
Explosive limits	upper = 66.4% lower = 15.5%
Solubility	miscible with most organic solvents, slightly soluble in water (ACGIH, 1991)
Odor threshold	160 ppm (geometric mean) (AIHA, 1989)
Odor description	sweet, pleasant, chloroform-like odor
Metabolites	carbon monoxide (Reprotext, 1999)
Conversion factor	1 ppm = 3.47 mg/m³ @ 25°C

III. Major Uses or Sources

Methylene chloride (MC) is used in paint and varnish remover, in aerosols as a cosolvent or vapor pressure depressant, and in solvent degreasing and metal cleaning. It is also used in plastics processing and in extraction of fats and oils from food products.

IV. Acute Toxicity to Humans

Frequently reported effects following acute inhalation exposure to MC include CNS depression at concentrations of 1,000 ppm (3,500 mg/m³) or more and increased blood carboxyhemoglobin (COHb) content at lower concentrations due to metabolism of MC to carbon monoxide (Stewart *et al.*, 1972).

Twelve healthy adult volunteers exposed to 195 ppm (680 mg/m³) MC for 4 hours exhibited impaired performance on dual-task and auditory vigilance tests (Putz *et al*., 1976). The dual task test required sustained attention divided between two sources of visual stimuli, and the auditory vigilance test required subjects to report relative auditory signal intensity. Statistically significant decrements in performance were first noted after 90 minutes of exposure; increasing decrements in performance were observed with prolonged exposure. Blood COHb levels rose from 1.35% pre-exposure to 5.1% post-exposure. The study did not address subjective symptoms such as headache, nausea, or irritation of the nose and throat.

In another study, blood COHb levels were significantly elevated (approximately 1% pre-exposure to a mean of 10.1% one hour following cessation of exposure) in three subjects exposed to a mean airborne concentration of 986 ppm (3,400 mg/m³) MC for 2 hours (Stewart *et al*., 1972). All three subjects exhibited an altered visual evoked response, as compared to pre-exposure measurements; one of the subjects reported mild light-headedness and another reported speech difficulties.

In one case report, use of a MC-based tile remover in a poorly ventilated room resulted in acute renal tubular necrosis and elevated liver enzymes levels indicative of possible hepatotoxicity (Miller *et al*., 1985). Although COHb levels were not measured, in the opinion of the authors kidney biopsy findings indicated that mitochondrial anoxic damage may have been caused by substantially elevated COHb levels. Buie *et al*. (1986) described a case of diffuse pulmonary edema, pleural effusions, and hypoxia in a 34-year-old man following the use of furniture stripper containing MC.

Although animal studies have shown COHb-induced cardiovascular effects following MC exposure (Aviado *et al*., 1977), no such reports exist for humans. Studies of men with coronary artery disease and exercise-induced angina report a decrease in time to onset of exercise-induced angina following exposure to carbon monoxide (CO) at concentrations sufficient to result in blood COHb levels of about 2% (Kleinman *et al*., 1989; Allred *et al*., 1989). From a physiologically based pharmacokinetic model of MC and CO it was estimated that a 1-hour exposure to 340 ppm (1,200 mg/m³) MC at a ventilation rate of 9 liters/min would result in a peak blood COHb level of 2% (Andersen *et al*., 1991; Reitz, 1994). The California Ambient Air Quality Standard for CO is based on a blood COHb level of 2% (CARB, 1982).

Predisposing Conditions for Methylene Chloride Toxicity

Medical: Pregnant women and fetuses may be at increased risk for adverse effects following methylene chloride exposure due to the greater affinity of fetal hemoglobin for CO. Persons with pre-existing cardiovascular disease might have increased sensitivity (Reprotext, 1999).

Chemical: Tobacco smokers typically have chronically elevated COHb levels and may not be able to tolerate higher levels of CO resulting from methylene chloride exposure.

V. Acute Toxicity to Laboratory Animals

The 20-minute LC_{50} for mice is 27,000 ppm (94,000 mg/m³) MC (Aviado *et al*., 1977). The 6-hour LC_{50} for guinea pigs is 12,000 ppm (42,000 mg/m³) MC (Balmer *et al*., 1976).

Hepatocyte lesions were observed at necropsy in mice exposed continuously for 12 hours to 5,000 ppm (20,000 mg/m³) MC (Weinstein *et al*., 1972). Rats exposed for 24-hours to 1,000 ppm MC exhibited significant decreases in duration of REM sleep compared to pre-exposure measurements (Fodor and Winneke, 1971). Non-significant deviations from pre-exposure sleep patterns were observed in rats exposed for 24 hours to 500 ppm (2,000 mg/m³) MC.

Mortality in mice challenged with an aerosolized streptococcal infection following exposure to 100 ppm (350 mg/m³) MC for a single 3-hour period was significantly greater than in unexposed mice (Aranyi *et al*., 1986). Significantly reduced pulmonary bactericidal activity, thought to be due to impaired macrophage function, was observed in mice following a 3-hour exposure to 100 ppm MC. No such effects were observed in mice exposed to 50 ppm (170 mg/m³) MC for a single 3-hour period.

Persistent myocardial arrhythmia and decreased cardiac output were observed in anesthetized open-chested dogs following a 5-minute inhalation exposure to 87 mg/m³ (25 ppm) MC (Aviado *et al*., 1977).

VI. Reproductive or Developmental Toxicity

An increased odds ratio (OR) of borderline significance (OR 2.3; 95% CI = 1.0-5.7) for spontaneous abortion was reported among female pharmaceutical workers exposed to MC (Taskinen *et al*., 1986). The range of exposure concentration was not reported.

Increased liver weights were noted in female rats exposed to 4,500 ppm (16,000 mg/m³) MC 6 hours per day for 3 weeks prior to mating and during the first 17 days of gestation (Hardin and Manson, 1980). Blood COHb levels were elevated to 7.2-10.1% (baseline measurements were not reported). Fetuses from exposed rats exhibited significantly decreased birth weights compared to controls, but no significant increases in soft tissue or skeletal anomalies were observed.

In rats and mice exposed for 7 hours per day on days 6-15 of gestation to 1,250 ppm (4,300 mg/m³) MC, a significant increase in maternal blood COHb levels was observed after the third 7-hour exposure (Schwetz *et al*., 1975). The incidence of delayed sternebral ossification was significantly greater in exposed rat pups compared to controls. Of note, control rat pups exhibited a greater number of litters with delayed ossification of lumbar ribs or spurs than exposed rats. In exposed mice, a significant number of litters contained pups with a single extra center of ossification in the sternum. The previously mentioned effects reflect developmental variation and are not adverse effects. No teratogenic effects were observed.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 4 ppm (14,000 μg/m³)

Study	Putz *et al*., 1976
Study population	twelve healthy adult volunteers
Exposure method	inhalation of 195 ppm methylene chloride
Critical effects	impaired performance on dual-task and auditory vigilance tests
LOAEL	195 ppm
NOAEL (LOEL)	not observed
Exposure duration	90 minutes
Extrapolated 1 hour concentration	240 ppm (195^2ppm* 1.5 h = C^2 * 1 h) (see Table 12 for information on "n")
LOAEL uncertainty factor	6
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	60
Reference Exposure Level	4 ppm (14 mg/m³; 14,000 μg/m³)

In twelve healthy adult volunteers exposed to 195 ppm (680 mg/m³) MC (Putz *et al*., 1976), significant decrements in performance were first noted after 90 minutes of exposure with increasing decrements in performance observed after prolonged exposure. Blood COHb levels rose from 1.35% pre-exposure to 5.1% post-exposure. No subjective symptoms, such as headache, nausea, or irritation of the nose and throat were reported. . The 90-minute exposure to 195 ppm MC is a LOAEL. An uncertainty factor of 6 was applied to the LOAEL to develop a NOAEL and a factor of 10 was applied to the NOAEL to account for individual variability in response. An equivalent 60-minute exposure was estimated from the 90-minute exposure using the equation $C^n * T = K$, where n = 2.

Cardiac effects resulting from COHb formation following MC exposure, such as those observed in sensitive human populations following carbon monoxide exposure (Kleinman *et al*., 1989; Allred *et al*., 1989), were considered as a possible endpoint of MC toxicity not yet identified in the human toxicological literature. A 2% COHb level results in decreased time to onset of exercise-induced angina in coronary artery disease patients. Based on an available model of blood COHb formation following MC exposure (Andersen *et al*., 1991), exposure to MC at a concentration of 340 ppm (1200 mg/m³) for 1 hour would result in a blood COHb level of 2%. This is higher than the exposure concentration resulting in the behavioral effects reported by Putz *et al*. (1976). Since angina is considered a severe adverse effect, this latter concentration should be considered when there is a sufficent database to derive a severe adverse effect level.

Level Protective Against Severe Adverse Effects

No recommendation is made due to the limitations of the database.

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

NIOSH (1995) lists a (revised) IDLH for methylene chloride of 2,300 ppm. However, NIOSH notes one report that a 10-minute exposure at 2,330 ppm produced vertigo and also quotes another reliable source which reported no feeling of dizziness after 1 hour of exposure to 2,300 ppm. NIOSH further states that 2 other authors report that no dizziness, but slight nausea, is caused by exposure to 2,300 ppm for 1 hour and that methylene chloride is not lethal at 25,000 ppm, but the citation gives only the authors' names. Thus it was not possible to refer to the original articles.

VIII. References

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